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Factors associated with sharing email information and mental health survey participation in large population cohorts

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Abstract

Background

People who opt to participate in scientific studies tend to be healthier, wealthier, and more educated than the broader population. While selection bias does not always pose a problem for analysing the relationships between exposures and diseases or other outcomes, it can lead to biased effect size estimates. Biased estimates may weaken the utility of genetic findings because the goal is often to make inferences in a new sample (such as in polygenic risk score analysis).

Methods

We used data from UK Biobank, Generation Scotland, and Partners Biobank and conducted phenotypic and genome-wide association analyses on two phenotypes that reflected mental health data availability: (1) whether participants were contactable by email for follow-up and (2) whether participants responded to follow-up surveys of mental health.

Results

In UK Biobank, we identified nine genetic loci associated ($P < 5 \times 10^{-8}$) with email contact and 25 loci associated with mental health survey completion. Both phenotypes were positively genetically correlated with higher educational attainment and better health and negatively genetically correlated with psychological distress and schizophrenia. One SNP association replicated along with the overall direction of effect of all association results.

Conclusions

Recontact availability and follow-up participation can act as further genetic filters for data on mental health phenotypes.

Keywords/MeSH: selection bias, cohort studies, mental health, follow-up studies, genome-wide association study, UK Biobank, Generation Scotland, Partners Biobank

Key Messages

- Large cohort studies show a "healthy volunteer bias" and this type of selection bias has a polygenic basis.
- Participants who take part in follow-up studies of mental health differ from participants who do not, and tend to be healthier, better education, and have a family history of dementia and/or depression.
- Genetic factors that positively associate with follow-up survey participation are positively related to cognitive function and psychological well-being and negatively related to psychiatric disorders.

Introduction

Selection bias in epidemiological and cohort studies occurs when characteristics of individuals that influence their likelihood of becoming or remaining as study participants are also related to exposure to risk factors or to outcomes of interest [1]. Selection bias can be introduced at many stages of a study, including at recruitment, at follow up, during record linkage, or in non-response to questionnaires or tasks and has the potential to lead to misestimates of phenotypic and genetic associations [2]. For example, a longitudinal study of psychiatric traits identified several characteristics related to loss-to-follow-up including age; education; ancestry; geographic location; and the presence, severity, and comorbidity of anxiety and depression [3]. There are several methods for handling selection bias if and when it needs to be taken into consideration. When all variables that influence selection and attrition are known, then bias can potentially be reduced or eliminated by conditioning on known variables or including

them as predictors [4]. In longitudinal studies, techniques such as inverse probability weighting, where observations that are similar to those that were lost to follow-up contribute proportionally more to the analysis, can be used to correct for selection bias [5]. Given the importance of selection bias on inference, it is crucial to fully characerise it in any given study population.

Initial ascertainment and recontact have been demonstrated to have a genetic basis. For example, individuals who had a high genetic risk of schizophrenia (calculated from polygenic risk scores) were less likely to complete follow-up questionnaires or attend additional data collection sessions [6]. and genetic propensity for other traits have similar effects[7]. Participation in large cohort studies is already known to have a "healthy volunteer" effect [8], so we sought to characterise the phenotypic and genetic correlates of participation in follow-up studies focused on assessing mental health traits. To this end, we analysed recontact and participation in three studies: the Mental Health Questionnaire (MHQ) online follow-up in UK Biobank [9] (N = 371 417 - 373 478), the Stratifying Resilience and Depression Longitudinally (STRADL) study in Generation Scotland [10] (N = 19 994), and the Partners Biobank [11] (N = 15 925). We conducted phenotypic and genome-wide association analyses in UK Biobank to determine how participants who completed the MHQ differed from the rest of the sample. We also analysed factors related to whether UK Biobank participants were contactable by email, as email invitations were the primary method of recruitment into the MHQ follow-up. We used participation in the STRADL questionnaire follow-up in Generation Scotland and a health information survey follow-up questionnaire in the Partners Biobank as replication data sets for genetic findings.

Conducting genetic analyses of selection bias and loss-to-follow-up can complement and add to existing knowledge gained by comparing biobank cohorts to

national statistics and published disease incidences and by comparing follow-up responders and non-responders on key characteristics. A participant's decision to continue to engage in a research study is likely to be multifactorial. Genetic analyses are a pragmatic first step in indicating what the many contributing factors are since genome-wide association summary statistics can be efficiently compared to those from hundreds of other studies. Genetic analyses can be revealing in other ways. First, genetic and environmental factors may have different magnitudes or directions of association with follow-up participation. Thus, genetic studies of follow-up samples may differ in the degree to which they are susceptible to selection bias compared to phenotypic studies. Second, a genetic study makes it possible to evaluate selection bias from traits that are only measured in a follow-up sample. For example, the Mental Health Questionnaire in UK Biobank includes evaluations of depression, anxiety, addiction, and trauma that were not measured at baseline, so it is not possible to directly compare responders and non-responders on these traits. Comparisons between responders and non-responders can even be made for traits that are rare or not even measured in the biobank. Genetic analyses can be correlated with external genome-wide summary statistics to elucidate the role of liability to disorders that are rare in most biobank samples, such as anorexia and schizophrenia. Finally, genetic summary statistics for follow-up response in a large sample in UK Biobank can become the basis for the analysis of selection bias in other genetic cohorts.

Methods

Samples

UK Biobank (UKB) is a population-based study of health in middle-aged and older individuals (N = 502 616). Eligible participants were aged 40 to 69 and recruited from 22 assessment centres in the United Kingdom. UK Biobank received ethical approval

from the Research Ethics Committee (reference 11/NW/0382). The present study was conducted under UK Biobank application 4844.

Generation Scotland: Scottish Family Health Study (GS:SFHS) is a family-based cohort (N = 24 091) recruited through general practitioners in Scotland [12, 13]. Eligible participants were aged 18 years or older who were able to recruit one or more family members into the study. GS:SFHS received ethical approval from the Tayside Research Ethics Committee (reference 05/S1401/89).

Partners Biobank: The Partners Biobank is a hospital-based cohort study from the Partners HealthCare hospitals with electronic medical records and genetic data supplemented with electronic health and lifestyle surveys [11]. Recruitment started in 2010 (N=78 726 in 2018) and is ongoing at participating across several clinics including Brigham and Women's Hospital and Massachusetts General Hospital. All participants provided consent upon enrolment. The current analysis was restricted to adults ≥18 years of age and of European ancestry[14] with high-quality genotyping data at the time of analysis.

Recontact and participation measures

During recruitment and baseline assessment (2006-2010), UKB participants were given the option of supplying an email address for receiving newsletters and invitations for online follow-up assessments. Of the 317 785 participants who supplied an email address, 294 738 provided a usable one while the remaining 23 047 either provided a syntactically incorrect or non-existent email address or asked that their email address be withdrawn. An email address was not provided by 184 831 UKB participants during baseline assessment. While this variable is called "email access" in the UK Biobank documentation (field 20005), we refer to this phenotype as "email contact". Although additional UK Biobank participants have subsequently provided an email address for

recontact , here we analyse the baseline availability of email contact so that it can be related to other baseline factors that were captured contemporaneously.

Starting in 2016, UKB participants who had provided email contact were sent an invitation to an online Mental Health Questionnaire (MHQ) entitled "thoughts and feelings" [9]. Participants who had not started the questionnaire or had only partially completed it were sent reminder emails after two weeks and again after four months. Participants also received information about the MHQ in a postal newsletter with instructions on how to participate. From data supplied by UK Biobank on 12 June 2018, 157 396 participants had completed the MHQ. Responses to the MHQ were submitted between July 2016 and July 2017. Mean time between baseline assessment and MHQ follow-up was 7.5 years (range 5.9–11.2 years). We refer to this phenotype as “MHQ data”.

In 2015, GS:SFHS participants were sent a questionnaire package by post as part of the Stratifying Resilience and Depression Longitudinally (STRADL) project with the aim of studying psychological resilience [10]. Participants were eligible for follow up if they had consented to recontact and if they had a Community Health Index (CHI) number. Of the 21 525 eligible participants, 9618 responded to the questionnaire, from which we coded a “STRADL data” phenotype.

In the Partners Biobank, following enrolment, participants were invited to complete the Partners Biobank Health Information Survey, an optional online lifestyle, environment, and family history survey[14]. Of the 15 925 participants of European ancestry with genetic data at the time of analysis, 6639 responded to the questionnaire.

Phenotype analysis

Demographic and health differences between responders and non-responders to the STRADL survey have been analysed previously and found that, among other differences, participants who were women, non-smokers, or who had low levels of psychological distress were more likely to respond. We thus first conducted a similar analysis in UK Biobank. We ran logistic regressions for email contact and MHQ data using R 3.5.0 [15]. We examined associations with age at initial assessment, sex, geographic region, educational qualification, smoking, alcohol consumption, number of diagnoses in linked electronic health records, and family history of dementia and depression (see Supplementary Information for regression input coding).

Genome-wide association, LD Score analysis, and replication analysis

We conducted genome-wide association studies (GWAS) on the UKB email contact and MHQ data phenotypes and conducted gene-based association and gene-set analyses (see Supplementary Information). We calculated a genomic control factor (λ_{GC})[16] for each set of GWAS results, which measures the inflation in test statistics above what would be expected by chance. Inflation in test statistics can caused both by a large number of genetic variants having an association with each trait (polygenicity) or by confounding factors, including population stratification and relatedness within the sample. We used LD score regression [17] to distinguish polygenicity from confounding. LD score regression exploits the increase in association test statistics for genetic loci that are closely linked in the region surrounding each causal genetic variant (indicating polygenicity) from confounding, which is expected to inflate test statistics evenly across the whole genome. The intercept from an LD score regression quantifies the test statistic inflation from confounding factors, where an intercept estimate close to 1.0 indicates no confounding. We also used LD Score regression to estimate the proportion

of variance in these traits attributable to common genetic variants (also referred to as SNP heritability) and calculated genetic correlations with 235 traits using LD Hub. We used False Discovery Rate to correct for multiple testing. To test for possible effects of mortality on loss-to-follow-up, we used the death register to identify participants whose death occurred before the MHQ assessment (N = 10 623). We then ran a GWAS on MHQ data with these participants removed.

In the replication data sets (Generation Scotland and Partners Biobank) we first tested for replication of independent SNPs (r^2 = 0.1, 250kb window) after Bonferroni correction. We calculated the expected power of replication using the GAS power calculator[18]. Following that, we tested for replication of direction of effect by performing a binomial test for the number of SNPs with the same direction of effect between the UK Biobank and Partners association results. We also calculated LD Score genetic correlations[17] between the UK Biobank and Generation Scotland summary statistics to estimate genome-wide similarity in phenotypes between these studies.

Results

Phenotypic associations of email contact and mental health follow-up (MHQ) data in UK Biobank

We conducted logistic regressions on email contact (valid Email address provided vs no valid Email address provided) and MHQ participation (those that had completed the MHQ vs those that had not completed the MHQ) in UK Biobank, examining the effects of age, sex, geographic region, educational attainment, alcohol consumption, smoking status, and personal and family history of disease. We retained participants with complete data for analysis (*N* = 373 478). Odds ratios from the logistic regressions are listed in Table 1. Women in UK Biobank were less likely to have provided an email

address but more likely to take part in the MHQ. There was regional variation in email contact and MHQ data. Individuals who attended assessment centres in Greater London and the South West of England were the most likely to have provided an email address while individuals from assessment centres in the North East of England and Scotland were the least likely. Individuals with greater educational attainment, those who were not current smokers, those with a fewer number of hospital diagnoses, and those with a family history of dementia or severe depression were more likely to have email contact and to have MHQ data.

Table 1. Logistic regression on email contact and MHQ data in UK Biobank (N = 373 478). Regression coefficients are expressed as odds ratios (OR) for increased probability of having email contact and increased probability of having MHQ data. CI = confidence interval

			Email contact		MHQ data	
	Variable	**N**	**OR (SE)**	**95% CI**	**OR (SE)**	**95% CI**
	Age (SD)	373478	0.85 (0.004)	0.846-0.861	1.01 (0.004)	0.998-1.014
Sex	Female	211768	1	---	1	---
	Male	161710	1.11 (0.010)	1.093-1.131	0.90 (0.008)	0.883-0.914
Region	East Midlands	25307	1	---	1	---
	Greater London	50795	1.85 (0.032)	1.785-1.909	1.13 (0.022)	1.088-1.173
	North East	27594	0.49 (0.008)	0.470-0.501	0.87 (0.018)	0.835-0.904
	North West	54053	0.81 (0.013)	0.781-0.833	0.84 (0.012)	0.817-0.866
	Scotland	27557	0.42 (0.009)	0.405-0.439	0.83 (0.017)	0.800-0.866
	South East	34114	0.84 (0.016)	0.805-0.867	1.13 (0.020)	1.088-1.165
	South West	33410	1.13 (0.021)	1.087-1.171	1.08 (0.020)	1.042-1.121
	Wales	15741	0.58 (0.013)	0.558-0.611	0.83 (0.020)	0.796-0.873
	West Midlands	33042	0.63 (0.011)	0.606-0.649	0.83 (0.016)	0.799-0.862
	Yorkshire	71865	1.00 (0.016)	0.967-1.028	0.93 (0.014)	0.900-0.957
Qualifications	None	53654	1	---	1	---
	GCSE	124377	2.35 (0.028)	2.297-2.408	2.29 (0.029)	2.230-2.342
	A Levels	44132	3.43 (0.048)	3.338-3.525	3.53 (0.057)	3.421-3.642
	Other	19583	2.53 (0.042)	2.451-2.616	2.72 (0.052)	2.620-2.823
	College/University	131732	4.27 (0.054)	4.163-4.375	4.43 (0.056)	4.322-4.541
Smoking	Never	210858	1	---	1	---
	Previous	126802	1.13 (0.009)	1.116-1.152	1.06 (0.008)	1.042-1.074
	Current	35818	0.71 (0.009)	0.689-0.723	0.73 (0.010)	0.706-0.744
Alcohol	Units/week (SD)	373478	1.05 (0.004)	1.038-1.053	1.03 (0.005)	1.021-1.039

Anthropometry	Body-mass index (SD)	373478	0.95 (0.004)	0.940-0.953	0.88 (0.004)	0.877-0.893
Diagnoses Yes vs No						
	Mental disorder	24668	0.75 (0.011)	0.729-0.774	0.68 (0.012)	0.654-0.701
	Injury	59706	0.90 (0.007)	0.881-0.909	0.83 (0.009)	0.815-0.851
	Other disease	278019	0.95 (0.009)	0.929-0.963	0.91 (0.009)	0.889-0.923
Family history Yes vs No						
	Alzheimer's/dementia	52238	1.18 (0.013)	1.157-1.208	1.22 (0.013)	1.198-1.250
	Severe depression	54651	1.04 (0.011)	1.022-1.066	1.11 (0.012)	1.084-1.131

Genome-wide association analysis of email contact and MHQ data in UK Biobank

After filtering UK Biobank individuals to a White British, unrelated sample, the sample size was N = 371 417 for the GWAS of email contact and N = 371 428 for the GWAS of MHQ data. After clumping, there were nine loci ($P \leq 5 \times 10^{-8}$) for email contact (Figure 1, Table 2, and Supplementary Table S1) and 25 for MHQ participation (Figure 2, Table 3, and Supplementary Table S11). The λ_{GC} was 1.29 for email contact and 1.37 for MHQ data. The LD score intercept for email contact and MHQ data in UK Biobank were 1.013 (SE 0.008) and 1.020 (SE 0.008) respectively. This yielded inflation ratios indicating that only 3.7% (SE 0.025) and 4.3% (SE 0.020) of the inflation in test statistics for email contact and MHQ data were caused by confounding factors and thus most of the inflation in test statistics was attributed to a large number of genetic loci influencing both traits (polygenicity).

Table 2. Top lead SNPs associated with email contact in UK Biobank. A1= effect allele, Freq. = frequency of A1 allele, OR = odds ratio, S.E. = standard error. Direction of effects are listed for the UK Biobank discovery sample and the Generation Scotland and Partners Biobank replication samples as either positive (+) or negative (-).

Chr	SNP	Location (Bp)	A1/A2	Freq.	OR (S.E.)	P-value	Direction
1	rs632180	234,758,181	T/C	0.70	0.973 (0.005)	2.0×10^{-8}	--+
2	rs7597665	34,420,702	C/T	0.29	1.031 (0.005)	1.1×10^{-9}	+++
2	rs1455343	199,519,691	T/G	0.38	0.974 (0.005)	2.2×10^{-8}	--+
3	rs73078357	48,695,834	C/T	0.12	1.038 (0.007)	4.5×10^{-8}	+++
3	rs111488606	49,864,924	CA/C	0.44	0.973 (0.005)	2.3×10^{-8}	---
5	rs6452788	87,712,913	A/G	0.24	1.032 (0.005)	2.9×10^{-9}	++-
5	rs4976602	167,843,998	A/G	0.11	0.96 (0.007)	2.7×10^{-8}	---
6	rs1487441	98,553,894	A/G	0.49	1.031 (0.005)	9.5×10^{-12}	+++
18	rs1788784	21,159,630	G/A	0.66	1.031 (0.005)	1.3×10^{-10}	+++

Figure 1. Manhattan plot of email contact in UK Biobank.

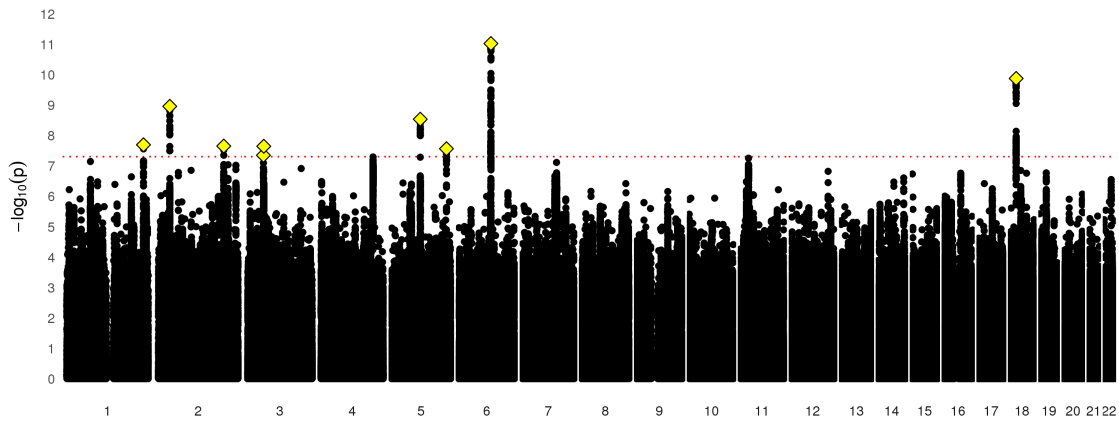
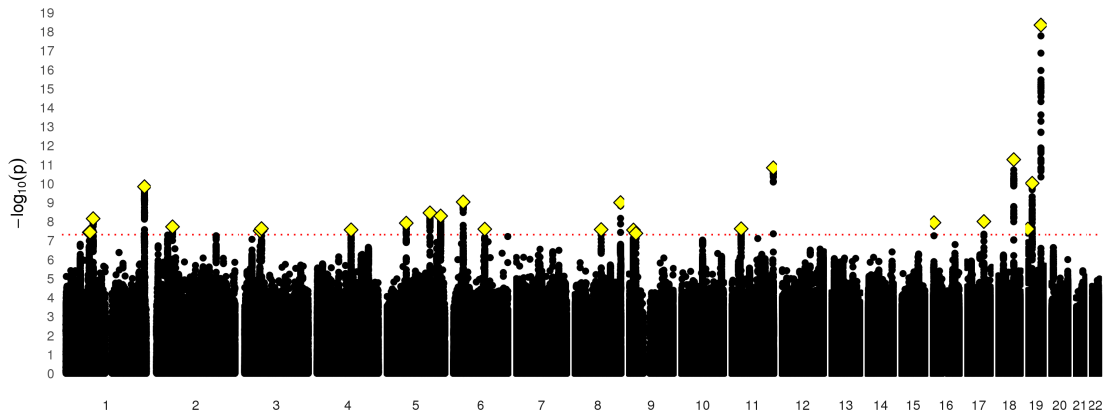


Table 3. Top lead SNPs associated with MHQ data. A1= effect allele, Freq. = frequency of A1 allele, OR = odds ratio, S.E. = standard error. Direction of effects are listed for the UK Biobank discovery sample and the Generation Scotland and Partners Biobank replication samples as either positive (+) or negative (-).

Chr	SNP	Location (Bp)	A1/A2	Freq.	OR (S.E.)	P-value	Direction
1	rs7542974	72,544,704	A/G	0.25	1.032 (0.006)	3.8×10^{-8}	+++
1	rs485929	74,678,285	G/A	0.39	1.028 (0.005)	3.7×10^{-8}	+-+
1	rs532246	84,411,238	G/A	0.74	0.968 (0.005)	7.0×10^{-9}	-+-
1	rs2789111	243,346,404	C/T	0.38	0.968 (0.005)	1.5×10^{-10}	--+
2	rs35028061	49,479,987	GT/G	0.38	1.029 (0.005)	1.9×10^{-8}	+--
3	rs9917656	48,581,513	C/T	0.30	1.03 (0.006)	3.2×10^{-8}	++-
3	rs13082026	52,962,681	T/C	0.44	0.972 (0.005)	2.4×10^{-8}	--+
4	rs57692580	106,214,476	A/T	0.39	0.973 (0.005)	2.8×10^{-8}	-++
5	rs34635	60,513,501	G/A	0.42	0.972 (0.005)	1.2×10^{-8}	---
5	rs146681214	133,867,867	AC/A	0.18	1.039 (0.007)	3.6×10^{-9}	+++
5	rs2336897	167,050,276	T/C	0.69	1.031 (0.005)	5.2×10^{-9}	++-
6	rs3993747	31,580,507	G/A	0.35	0.969 (0.005)	9.5×10^{-10}	---

6	rs59732267	98,432,302	CA/C	0.52	0.972 (0.005)	2.5×10^{-8}	---
8	rs28716319	83,269,854	G/A	0.28	1.031 (0.005)	2.7×10^{-8}	+-+
8	rs13262595	143,316,970	G/A	0.56	1.03 (0.005)	1.0×10^{-9}	+++
9	rs6474966	15,757,537	A/G	0.46	1.028 (0.005)	2.8×10^{-8}	+++
9	rs11793831	23,362,311	T/G	0.42	1.027 (0.005)	4.3×10^{-8}	+-+
11	rs1984389	31,740,989	C/A	0.54	0.973 (0.005)	2.4×10^{-8}	---
11	rs10791143	131,278,676	G/A	0.62	1.034 (0.005)	1.5×10^{-11}	+++
16	rs4616299	7,657,432	G/A	0.40	0.972 (0.005)	1.2×10^{-8}	---
17	rs56058331	56,427,128	A/G	0.42	1.029 (0.005)	1.0×10^{-8}	+++
18	rs1261078	52,866,791	G/A	0.05	0.927 (0.010)	5.6×10^{-12}	-+-
19	rs34232444	4,965,404	C/T	0.35	1.029 (0.005)	2.5×10^{-8}	++-
19	rs3746187	18,279,816	G/A	0.40	0.968 (0.005)	9.8×10^{-11}	---
19	rs429358	45,411,941	C/T	0.15	0.942 (0.006)	4.6×10^{-19}	---

Figure 2. Manhattan plot of data available in MHQ follow-up



Loci discovery and annotation of the Email contact and MHQ phenotypes

The nine loci associated with email contact were found to contain an overrepresentation of SNPs found in ncRNA intronic regions (57.5%), as well as SNPs found in intronic regions (28.4%) (Supplementary Figure S1 and Supplementary Table S1). Evidence was also found that these loci contained regulatory regions of the genome, indicated by 32.0% of the SNPs in the genomic loci having RegulomeDB (RDB) less than 2, indicating that genetic variation in these loci is likely to affect gene expression. Finally, 77.6% of the SNPs within the independent genomic loci had a minimum

chromatin state of < 8. This is further evidence that these loci are located in an open chromatin state and that they are located within regulatory regions. Using the GWAS catalogue, lead and tagging SNPs from these 9 independent genomic loci were found to overlap with loci previously associated with body mass index and obesity (2 loci), as well as with educational attainment and intelligence (3 loci). (Supplementary Table S2).

The 25 loci associated with the MHQ participation phenotype notably included rs429358, a missense mutation in *APOE*. The rs429358-C allele is a marker for APOE- ε4 genotype, and the direction of the effect for this SNP indicated that participants with more copies of APOE-ε4 were less likely to participate in the MHQ (OR = 0.942±0.0057SE for each additional ε4 copy). Functional annotation of the SNPs found within these regions showed that these SNPs were primarily located in introns (47.3%), and intergenic regions (17.7%) and 2.9% had no known function (Supplementary Figure S2 and Supplementary Table S8). Of these SNPs, 30.8% had an RDB score of less than 2 and 83.8% had a minimum chromatin value of less than 8 providing further evidence that these variants are located in regions of the genome that are linked to gene regulation. These 25 loci showed overlap with the loci identified in previous GWAS examining cognitive abilities and education (6 loci), Schizophrenia (5 loci), and Alzheimer's Disease (1 locus) (Supplementary Table S9).

Gene mapping of the Email access and MHQ phenotype

We used three strategies for mapping the SNPs in the associated loci to genes. First, positional mapping aligned the SNPs from the independent genomic loci associated with email contact to 20 genes by using location, whereas eQTL mapping matched cis-eQTL SNPs to 40 genes whose level of expression they have been shown to influence. Finally, chromatin interaction mapping annotated SNPs to a total of 41 genes,

using three-dimensional DNA-DNA interactions between the SNPs' genomic regions, and close or distant genes (Supplementary Tables S4 and S5, Supplementary Figure 5a–f). Collectively these mapping strategies identified 70 unique genes, of which 21 were implicated by two mapping strategies and 10 being implicated by all three. A total of five genes, *TNNI3K*, *LRRIQ3*, *NEGR1*, *FPGT*, and *FPGT-TNNI3K*, were implicated using all three methods and showed evidence of a chromatin interaction between two independent genomic risk loci (Supplementary Table S4). Gene-based statistics derived in MAGMA indicated a role for 72 genes (Supplementary Table S5), 4 of which overlapped with genes implicated by all three mapping strategies (Supplementary Figure S3).

For the MHQ data phenotype, positional mapping implicated 42 genes, with eQTL mapping indicating a role for 86 genes. Chromatin interaction mapping annotated a total of 124 genes (Supplementary Tables S14 and S15, Supplementary Figure S6a-m). Across these three mapping strategies, 181 unique genes were identified with 46 of these being implicated by two mapping strategies and 25 being implicated by all three MAGMA was also used and indicated a role for 81 genes (Supplementary Figure S4 and Supplementary Table S15). Fifteen of these 81 genes overlapped with those identified using the three mapping strategies.

Gene-set and gene property analysis

The presynaptic membrane gene-set was enriched for the Email contact phenotype ($P = 5.19\times10^{-7}$) (Supplementary Table S6). Gene property analysis showed a relationship between expression in the EBV-transformed lymphocyte cells ($P = 9.24\times10^{-4}$) and for gene expression in the early mid-prenatal time of life ($P = 0.004$) (Supplementary Tables S9 and S10).

For the MHQ data phenotype none of the gene sets were enriched (Supplementary Table S16). However, gene property analysis indicated a relationship between gene expression in the brain and the MHQ phenotype ($P = 2.64\times10^{-4}$) (Supplementary Table S17) when examining the specific tissue gene groupings this relationship was driven by expression change in the cerebellar hemisphere ($P = 8.52\times10^{-6}$) and the Cerebellum ($P = 1.27\times10^{-5}$) (Supplementary Table S18). A relationship between gene expression in the early prenatal lifespan range ($P = 0.002$) and the early mid-prenatal lifespan was also found ($P = 5.33\times10^{-4}$) (Supplementary Table S19).

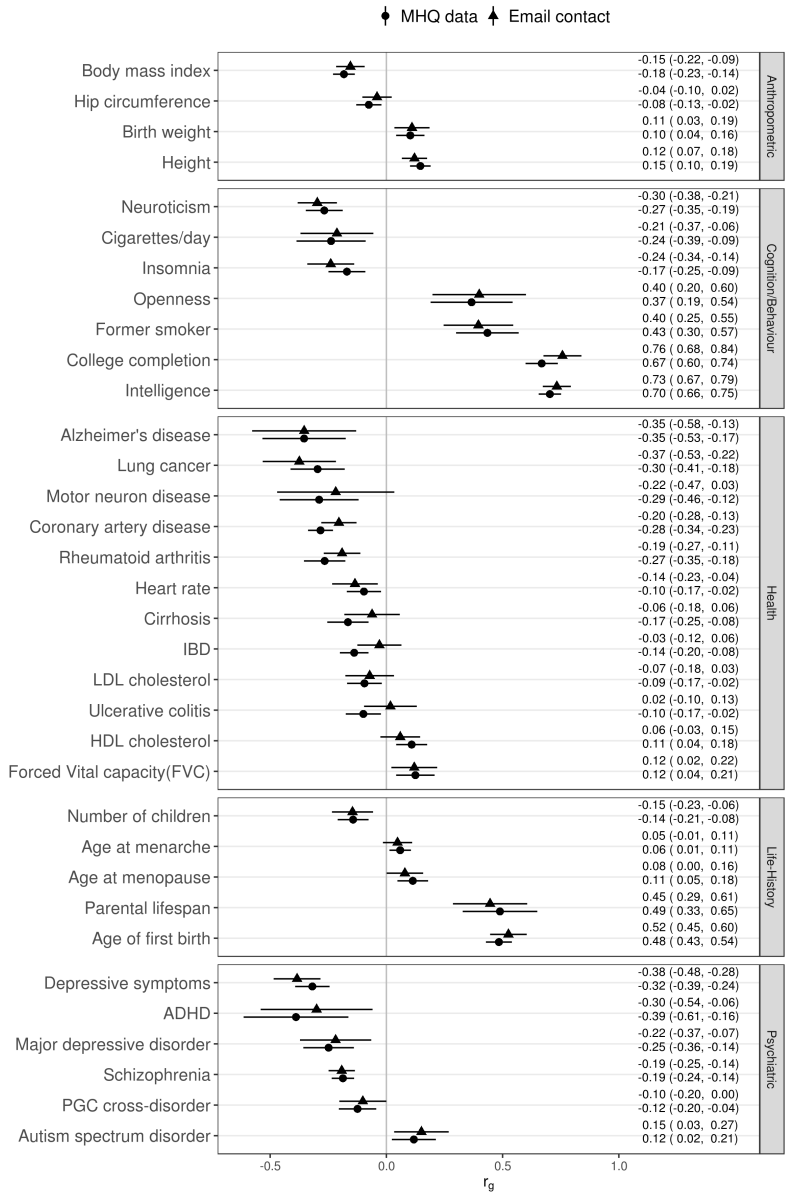
LD Score regression analysis

We used LD score regression to estimate SNP heritability from the GWAS results. Heritability on the liability scale for email contact was 0.073 (0.004SE) and for MHQ data was 0.099 (0.004SE). The genetic correlation between email contact and MHQ data was 0.822 (0.020SE).

We used LD Hub [19] to estimate genetic correlations with a large number of other traits. Both email contact and having MHQ data were genetically correlated with a broad spectrum of traits. Results for an illustrative set of traits is plotted in Figure 3 and the results for all traits are listed in Supplementary Table S21. For most anthropometric, behavioral, cognitive, psychiatric, health-related, and life-history traits the direction of the genetic correlations with email contact and MHQ participation was the same. In general, genetic factors associated with providing an email address for recontact to UK Biobank and taking part in the MHQ were also associated with better health, higher intelligence, lower burden of psychiatric disorders, and a slower life-history (e.g., later

age at menarche, age at first birth, and age at menopause). Both email contact and MHQ participation were not genetically correlated with any traits categorized as bone, kidney, uric acid, and metals (transferrin/ferritin). Additionally, email contact was not genetically correlated with glycemic traits while MHQ data availability was not genetically correlated with hormone or metabolite phenotypes.

Figure 3. LD Score genetic correlations (r_g) with email contact (triangle) and MHQ data (circle), with 95% confidence intervals.



Effect of mortality on MHQ genetic associations

To test for the roll of mortality on our findings, we re-ran the genome-wide association analysis of MHQ data availability after removing participants whose dates of death occurred before the MHQ assessment. The overall inflation in association test statistics including and excluding deceased participants was identical (mean $\chi^2 = 1.438$) and the genetic correlation between the two sets of summary statistics was 0.9996 (SE = 0.0002). We compared the top independent associated SNPs in the GWAS in the larger sample to those that excluded deaths (Supplementary Table S24 and Figure S7). While there three SNPs that no longer passed the criterion for genome-wide significance, there was no appreciable change in the effect sizes estimates for any of the SNPs

.

Replication in Generation Scotland and Partners Biobank

We examined whether any of the associations results for the email and MHQ data phenotypes replicated in an independent sample, using whether members of Generation Scotland participated in the STRADL follow-up of mental health. At an alpha criterion of 0.05/34 and an average genotype relative risk of 1.015, there was 4% power to replicate in Generation Scotland and 2% power in Partners Biobank, and replicating the UK Biobank findings requires approximately 200,000 cases and controls to achieve 90% power.[18] None of the independent SNPs in the UKB GWASs replicated in Generation Scotland after Bonferroni correction (34 tests) (Supplementary Tables S22 and S23). We observed replication evidence for one independent SNP (rs9917656, 6.2×10^{-4}) in Partners Biobank after Bonferroni correction (Supplementary Tables S22 and S23). Between UK Biobank and Partners Biobank, more of the SNPs for survey participation had the same direction of effect than expected (20/25, exact binomial test

p-value = 0.002). Furthermore, the STRADL data phenotype was moderately genetically correlated with both UKB email contact (r_g = 0.430, SE = 0.112, p = 0.0001) and UKB MHQ data (r_g = 0.619, SE = 0.130, $p = 1.98 \times 10^{-6}$) and had a SNP heritability on the liability scale of 0.112 (SE 0.0408).

Discussion

Using data from UK Biobank, we found that individuals who provided an email address for recontact and who participated in follow-up surveys of mental health differed from those who did not with regards to demographic, psychological, health, and lifestyle, and genetic factors. The UK Biobank sample differs from the UK population [20], and our results show that ascertainment processes also exert an effect on follow up assessments. Most of the phenotypic and genetic associations were in the same direction. These results were not due to population stratification as only 4% of the inflation in GWAS statistics could be attributed to factors other than polygenic heritability. Having greater educational attainment, being a non-smoker or a former smoker, having fewer hospital diagnoses of illness or injury, and having a family history of dementia or a family history of serious depression all predicted greater likelihood of providing email contact information. Furthermore, those variables were also associated with providing responses to the online Mental Health Questionnaire (MHQ). Importantly for understanding the composition of the MHQ subset, having an inpatient diagnoses of a mental disorder was associated with lower participation rates in the MHQ (OR = 0.68, 95% CI = 0.65-0.70), and this was a larger effect size than other hospital diagnoses, specifically injury (OR = 0.83) and non-psychiatric disorders (OR =

0.91). A few effects went in the opposite direction between the email contact and MHQ data variables, with men and younger individuals more likely to provide an email address to UK Biobank, whereas women were more likely to provide MHQ data.

Email contact and MHQ data availability had SNP heritabilities of 7.3% and 9.9% respectively. We identified nine independent SNPs associated with email contact and 25 for MHQ data, more than for many GWAS studies of disease traits in the same sample. Loci for both phenotypes were mostly located within regulatory regions. Of particular interest was the association of apolipoprotein E (APOE) ε4 genotype, which is a major risk factor for Alzheimer's disease [21], with a decrease in participation in the MHQ follow-up. One SNP associated with MHQ data replicated in the Partners Biobank sample. The SNP, rs9917656, in an intron in the 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 (PFKFB4), a signally enzyme involved in switching between different forms of carbohydrate metabolism.[22]. However, several other genes are implicated in this locus by positional mapping (genomic locus 6 in Supplementary Table S13). Given the effect sizes found in the discovery sample, both Generation Scotland and Partners were underpowered for replicating association results. However, the consistent directions of effect in the Partners cohort and the strong genetic correlation between STRADL participation and the email contact and MHQ data phenotypes suggests that similar genetic factors are driving participation in follow-up studies.

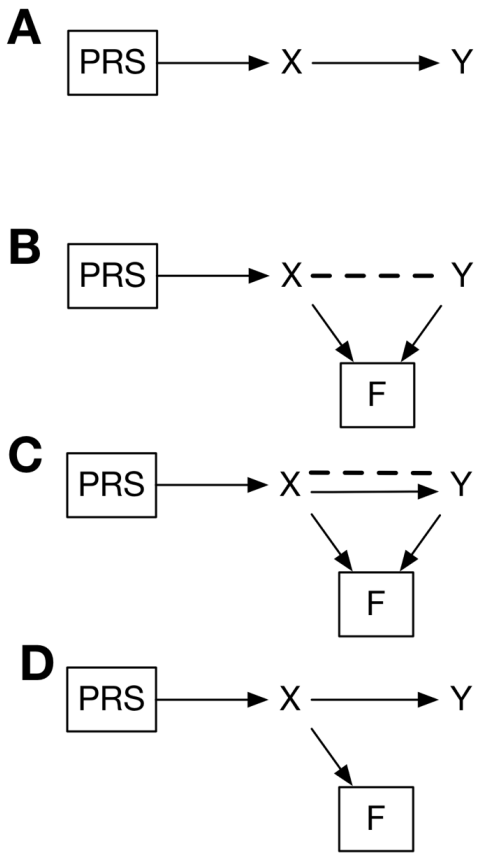
Email contact and MHQ data shared similar genetic correlations with other traits. There were strong genetic correlations between email contact and indicators of cognitive ability (college completion, r_g = 0.76; intelligence, r_g = 0.73). Contact and data availability were also genetically associated with a lower burden of genetic risk to mental illness and lower BMI. These results were in the same direction as the phenotypic analysis. The negative genetic correlation with schizophrenia matches

results from follow-up participation in the ALSPAC cohort using polygenic risk scores [6] and suggests that this association is not specific to schizophrenia.

The similarity in the results for phenotypic and genetic factors associated with email contact and MHQ data show that the availability of an individual to be contacted by email and their choice to participate both act as a filter for selection into the subsample of UK Biobank with Mental Health Questionnaire data. Notably, self-reports of a family history of dementia and a family history of severe depression were more common in email providers and MHQ completers, but individual genetic associations with both these disorders showed negative correlations. Individuals who reported dementia or severe depression in their family were therefore more likely to be MHQ participants, even though having a personal genetic predisposition to these disorders may also decrease their likelihood of participating. Knowledge of family history may be a strong motivational factor for participating in follow-up surveys of mental health.

Our sample was large enough that we were able to identify specific genetic loci that were related to participation in follow up studies of mental health. We were also able to analyse the genetics of one particular factor (the availability of email contact for receiving invitations) that is heavily involved in the specific process of follow-up participation. However, a limitation of our analysis is that information on email contact was available for participants at baseline only and thus did not distinguish the entire subset of participants who would have received an email invitation. Another limitation is that information from electronic health records only covered hospital admissions and thus would underestimate associations with milder health conditions. Our study also does not address factors that would differentially influence participation of individuals of non-European ancestry.

Figure 4. Possible effects of selection bias on polygenic risk score analyses in follow-up studies. *PRS* = Polygenic Risk Score, *X* and *Y* = phenotypes of interest, *F* = selection into follow-up, directional solid line = true causal association, dashed line = induced or attenuated statistical dependence**. A.** Causal model to be tested where PRS causes phenotype *Y* via phenotype *X* **B.** Worst-case scenario where PRS influences *X* but not *Y* and both phenotypes cause follow-up participation. Analysing only follow-up participants is the same as conditioning on *F*, which induces a correlation between PRS and *Y*. **C.** More likely scenario, where both *X* and *Y* cause follow-up participation. Conditioning on *F* attenuates estimates of the relationship between PRS and *Y*. **D.** Ideal scenario where *X* causes follow-up participation, but *Y* does not. Conditioning on *F* has no impact on the dependence of *Y* on PRS.



Individuals in large epidemiological cohorts who participate in follow-up surveys differ in their patterns of phenotypic and genetic association with traits of interest from those who do not. Because most factors had a consistent relationship with the two-step selection process (contactability by email and opting to participate in follow-up), it is likely that these same factors may also differentiate people who choose to become part of the cohort in the first place from other people in the larger population. These factors are very likely to bias the selection of individuals selected for inclusion in population-based studies towards those with positive family histories but lower personal genetic risk of mental health conditions such as depression and dementia. Analysing variables within a follow-up study may have the effect inducing statistical dependence or attenuating estimates of the relationships among variables [2]. Figure 4a illustrates a hypothesised causal model where a polygenic risk score (PRS) influences a phenotype or outcome *Y* via an intermediate phenotype *X*. This model could be tested by d-separation[23]: if the model is true, then regressing *Y* on *X* will result in conditional independence of PRS and *Y*. Figure 4b illustrates a scenario analysing the effect of the PRS where participation in follow-up is a collider for the two phenotypes when they do not have a causal relationship with each other. Analysing data only within the follow-up sample creates non-independence between the *X* and *Y* traits and thus between PRS and *Y*. Even when one trait causes the other, conditioning on follow-up participation can bias the estimate of PRS on the downstream trait (Figure 4c). A scenario where only one of the traits causes follow-up would not result in biased estimates of the effects of PRS (Figure 4d).

Going forward, studies should evaluate (e.g., using simulations [2]) the particular effects that selection and attrition might have on effect estimates and, where available, check results from follow-up assessments against those from baseline data, even in the

cases where the follow-up data provides better or more comprehensive measures of phenotypes of interest. Because continued participation in large cohorts studies recapitulates the "healthy volunteer" effect, comparing responders and non-responders in follow-up surveys may be a useful way to analyse how selection bias may influence the generalizability and accuracy of findings.

Data availability

Underlying study data is available to bona fide researchers from UK Biobank https://www.ukbiobank.ac.uk/, Generation Scotland http://www.generationscotland.org/, and Partners HealthCare Biobank https://biobank.partners.org.

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Supplementary Information

Logistic regression analysis input coding

We centered and standardized age. We determined geographic region by grouping the assessment centres together into regions of England (South East, South West, East Midlands, West Midlands, North West, North East, and Yorkshire), Greater London, Scotland, and Wales. Education, smoking, drinking, and family history were assessed by means of a touchscreen interview during the initial assessment. We categorized educational qualifications as None, Professional, Higher (college or university), Secondary (A levels, O levels, GCSEs, CSEs), and Vocational (NVQ, HND, HNC). Smoking history had the responses 'Prefer not to answer', 'Never', 'Previous', and 'Current'. For alcohol drinking, participants reported their average weekly and monthly consumption for different drink types from which we derived a measure of average alcohol consumption in units per week (Clarke et al., 2017) and standardized this variable for input into the model. For linked hospital records, we first removed diagnoses related to pregnancy (ICD-10 chapter O), congenital conditions (chapter Q), and health care provision (chapters U and Z). For the remaining diagnoses, we categorized them into mental health conditions and addictions (chapter F), injuries (chapter S, T, V, and Y), and all other diseases. Participants were assigned a value of 1 for each category if they had any diagnostic codes in that category. Participants with linked hospital records who did not have any incidences of a diagnostic category were assigned a count of 0.

Genotyping, genomic QC, and GWAS

UK Biobank contains genotype data imputed to ~92 million variants (Bycroft et al., 2018). We performed QC procedures on SNPs with filters for MAF > 0.001 and INFO > 0.1. We removed participants who had failed genotype platform QC, who did not cluster genetically as White British, or who overlapped with Psychiatric Genomics Consortium MDD and Generation Scotland participants; and we conducted additional filtering on related individuals (Howard et al., 2018). This resulted in 16 367 095 variants for 371 428 individuals for genetic analysis (Supplementary Figure S8). We conducted genome-wide association analyses using BGENIE v1.3 (Bycroft et al., 2018) that coded the outcome variables as 0/1 in a linear regression. We covaried for age, sex, assessment centre, genotyping platform, and 20 UKB-provided principal components. We approximated odds ratios for the SNP effects using the transformation to the log-odds scale, $\log(\mathrm{OR}) = \beta\ /(k\ (1\ -\ k))$, where k is the fraction of participants who were coded as 1 in the outcomes variable (email contact k = 0.6, MHQ data k = 0.33).

For Generation Scotland, 8 642 105 imputed variants were available for 19 994 participants (Hall et al., 2018). Variants with MAF < 0.005 and INFO < 0.8 were excluded. We performed association tests on the STRADL data phenotype using the mixed linear model with candidate marker excluded (MLMe) approach in GCTA v1.91.1 (Yang, Zaitlen, Goddard, Visscher, & Price, 2014). We constructed two GRMs using a leave-one-chromosome-out (LOCO) approach: one GRM that included all relationship coefficients and a second GRM that set relatedness to 0 when the relationship coefficients < 0.025 (Zaitlen et al., 2013). We fitted age and sex as covariates. To see if the results from the UKB phenotypes replicated, we looked up each independent significant SNP (or an LD proxy) in the GWAS of the STRADL data phenotype and assessed whether they were significant after Bonferroni correction. We also calculated the LD score genetic correlation of the STRADL data phenotype with the UKB email and MHQ data phenotypes.

For Partners Biobank, DNA from participants was genotyped using ~1.6 million SNPs on the Illumina Multi-Ethnic GWAS/Exome SNP Array and imputed using Minimac3 using the HRC (Version r1.1 2016) reference panel (Dashti, Redline, & Saxena, 2018). Replication was sought for the 35 identified signals (or an LD proxy). Individual SNPs association analyses were conducted using logistic regression analyses and an additive genetic model in PLINK adjusted for age, sex, genotyping array, and principal components of ancestry. Associations were considered significant after Bonferroni correction.

Loci discovery and functional annotation

Genomic risk loci were derived using clumping, carried out in FUnctional Mapping and Annotation of genetic associations (FUMA) (Watanabe, Taskesen, van Bochoven, & Posthuma, 2017). First, FUMA was used to identify independent significant SNPs using the *SNP2GENE* function. SNPs with a P-value of $\leq 5 \times 10^{-8}$ and independent of other genome wide significant SNPs at $r^2 < 0.6$ were identified from the summary GWAS statistics of the UKB email contact and MHQ data phenotypes. Second, using these independent significant SNPs, candidate SNPs were identified as all SNPs that had a MAF > 0.001 and were in LD of $\geq r^2$ 0.6 with at least one of the independent significant SNPs. These candidate SNPs included those from the UK10K/1000G and the haplotype reference consortia panel (UK Biobank release 1) and may not have been included in the UKB GWASs. Third, lead SNPs were identified using the independent significant SNPs. Lead SNPs were defined as SNPs that were independent from each other at r^2 0.1. Finally, genomic risk loci that were 250kb or closer were merged to form a single locus.

The lead SNPs identified above, and those in LD with the lead SNPs, were then mapped to genes using ANNOVAR and the Ensemble genes build 85. Intergenic SNPs were mapped to the two closest up- and downstream genes which can result in them being assigned to multiple genes. eQTL mapping was performed using each independent significant SNP and those in LD with it. Those SNP-gene pairs that were not significant (FDR ≤ 0.05) were omitted from the analysis.

Gene-mapping

Genetic variation in each of the independent genomic loci was mapped to genes using three complementary strategies. First, positional mapping was used to map SNPs to genes based on physical distance. SNPs within a 10kb window from the known protein genes found in the human reference assembly (hg19). Second, expression quantitative trait loci (eQTL) mapping was carried out by mapping SNPs to genes if allelic variation at the SNP was associated with expression levels of the gene. For eQTL mapping information on 45 tissue types from three data bases (GTEx, Blood eQTL browser, BIOS QTL browser) based on cis-QTLs where a SNPs are mapped to genes up to 1Mb away. A false discovery rate (FDR) of 0.05 was used as a cut off to define significant eQTL associations.

Finally, chromatin interaction mapping was carried out to map SNPs to genes when there is a three-dimensional DNA-DNA interaction between the independent genomic risk loci with a gene region. Chromatin interactions can involve long-range interactions between SNPs with genes as such no genomic distance boundary is applied. Hi-C data of 14 tissue types was used for chromatin interaction mapping. Chromatin interactions can also span multiple genes, and SNPs can be located in a region that interacts with other regions also containing multiple genes. In order to both reduce the number of genes mapped, and to increase the probability that those genes mapped are biologically linked to genetic variation at the independent genomic loci, only genes where one region involved with the interaction overlapped with a predicted enhancer region in any of the 111 tissue/cell types found in the Roadmap Epigenomics Project (Bernstein et al., 2010), and the other region was located in a gene promoter region (250bp upstream and 500bp downstream of the transcription start site and also predicted to be a promoter region by the Roadmap Epigenomics Project) were included here. An FDR of 1×10^{-5} was used to define a significant interaction.

Gene-based GWAS

Gene-based analyses have been shown to increase the power to detect association due to the multiple testing burden being reduced, in addition to the effect of multiple SNPs being combined. Gene-based GWAS was conducted using MAGMA (de Leeuw, Mooij, Heskes, & Posthuma, 2015), also implemented in FUMA (Watanabe et al., 2017). Regardless of P-value, all SNPs located within protein coding genes were used to derive a P-value describing the association between genetic variation across the gene with either email or questionnaire. The NCBI build 37 was used to determine the location and boundaries of 18 877 autosomal genes and linkage disequilibrium within and between genes was gauged using the UK Biobank 1 reference panel. A Bonferroni correction was applied to control for the number of genes tested.

Gene-set analysis

A competitive gene-set analysis was conducted in MAGMA to identify the biological systems vulnerable to perturbation by common genetic variation. Competitive testing examines if genes within the gene set are more strongly associated with the trait of interest than genes from outside the gene set, and differs from self-contained testing by controlling for type 1 error rate as well as being able examine the biological relevance of the gene-set under investigation.

A total of 10 894 gene-sets (sourced from Gene Ontology, Reactome, and, MSigDB) were examined for enrichment. To control for the 10,894 gene sets examined, a Bonferroni correction was applied.

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Supplementary Figures

Figure S1. Functional categories, RDB scores, and minimum chromatin states for independent risk loci associated with UKB email contact.

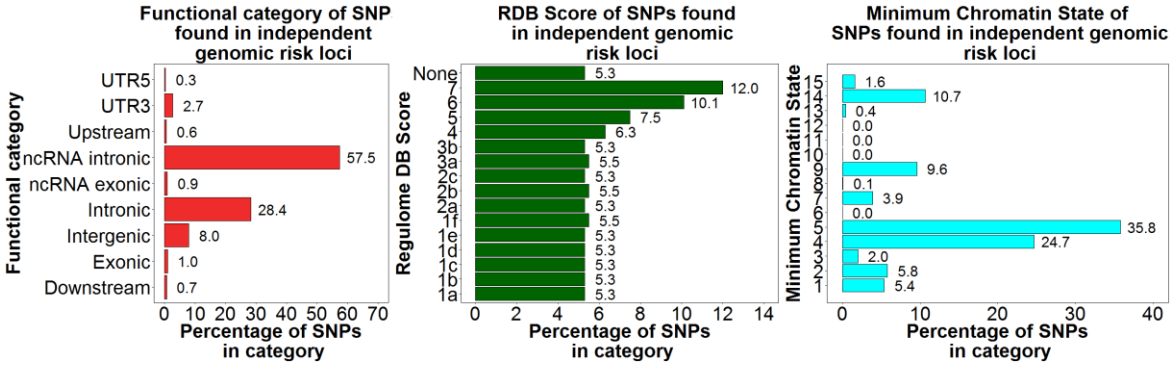


Figure S2. Functional categories, RDB scores, and minimum chromatin states for independent risk loci associated with UKB MHQ participation.

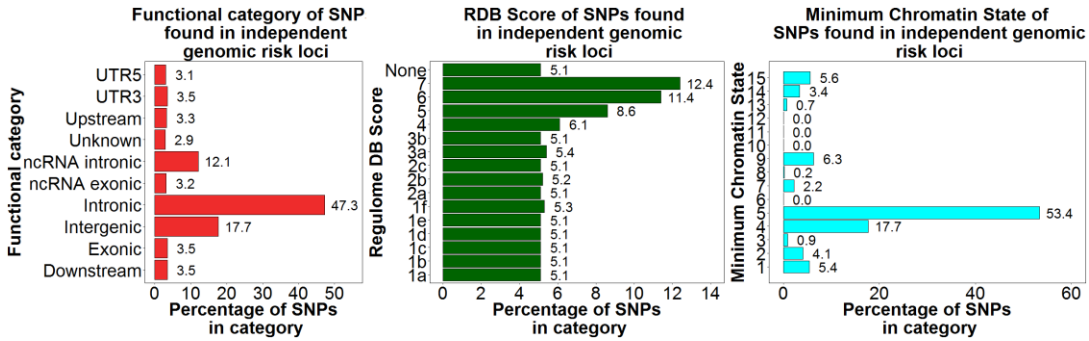


Figure S3. Number of genes implicated by different mapping strategies for UKB email contact.

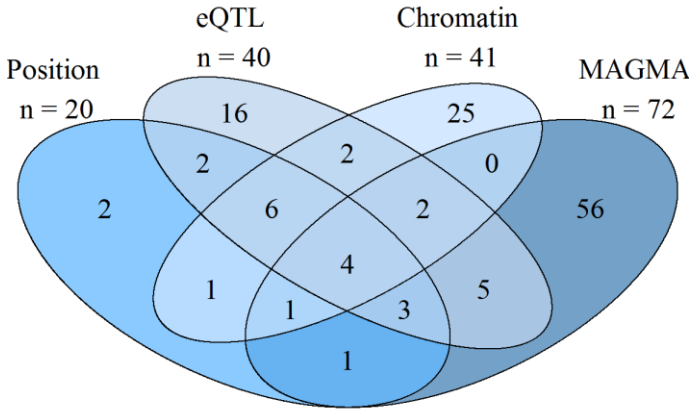
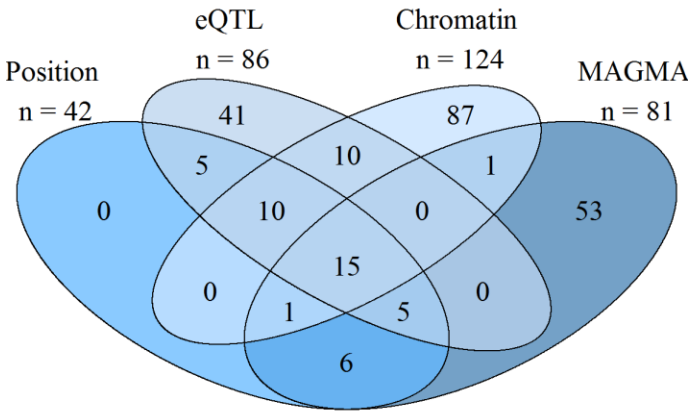


Figure S4. Number of genes implicated by different mapping strategies for UKB MHQ data.



Supplementary Figures S5 and S6.

Circos plots by chromosome illustrating genome-wide significant loci associated with the Email contact and the MHQ data phenotype are shown. For each phenotype the most outer layer shows the Manhattan plot and only SNPs where P <0.05 are shown. Each of the SNPs in the genomic risk loci are colour coded indicating the maximum r^2 with one of the independent significant SNPs in the locus with red indicating the highest r^2 and blue the lowest r^2(red r^2>0.8, orange r^2>0.6, green r^2>0.4, and blue r^2>0.2). SNPs shown in grey are not in LD with any of the genome wide significant SNPs. The rsID of the most significant lead SNP in each loci is shown. The second layer is the chromosomal ring with the independent genomic risk loci highlighted in blue. Next, the genes mapped by chromatin interactions or eQTLs are displayed. Genes mapped using chromatin interactions the gene is displayed in

orange, with genes mapped by eQTL shown in green. Genes that are displayed in red are those mapped using both chromatin interactions and eQTLs. Chromatin interaction links (coloured orange for chromatin interactions and green for eQTLs are displayed.

Figure S5a. Circos plot for email contact chromosome 1

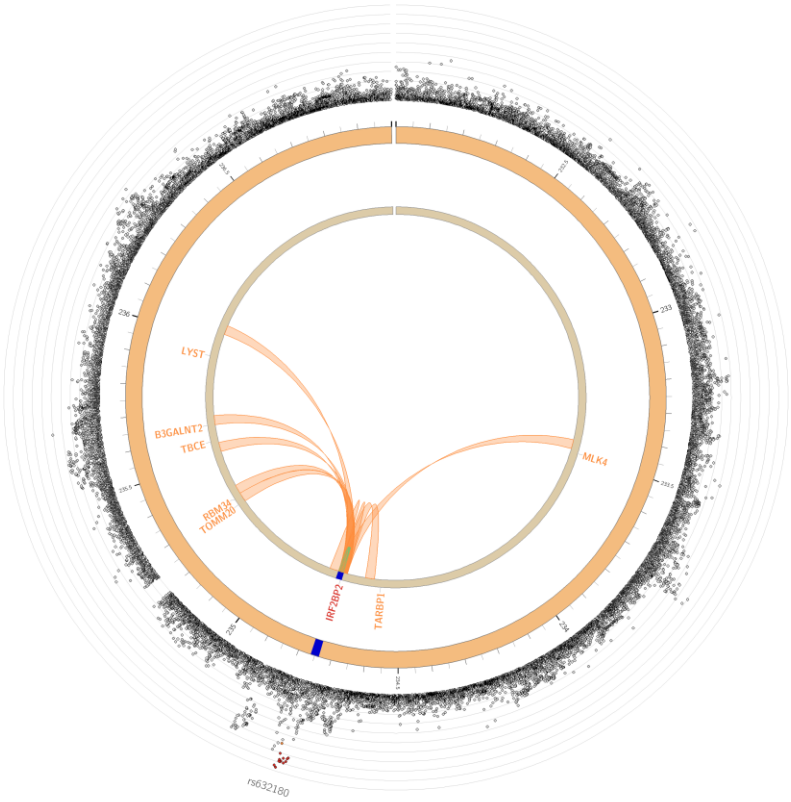


Figure S5b. Circos plot for email contact chromosome 2

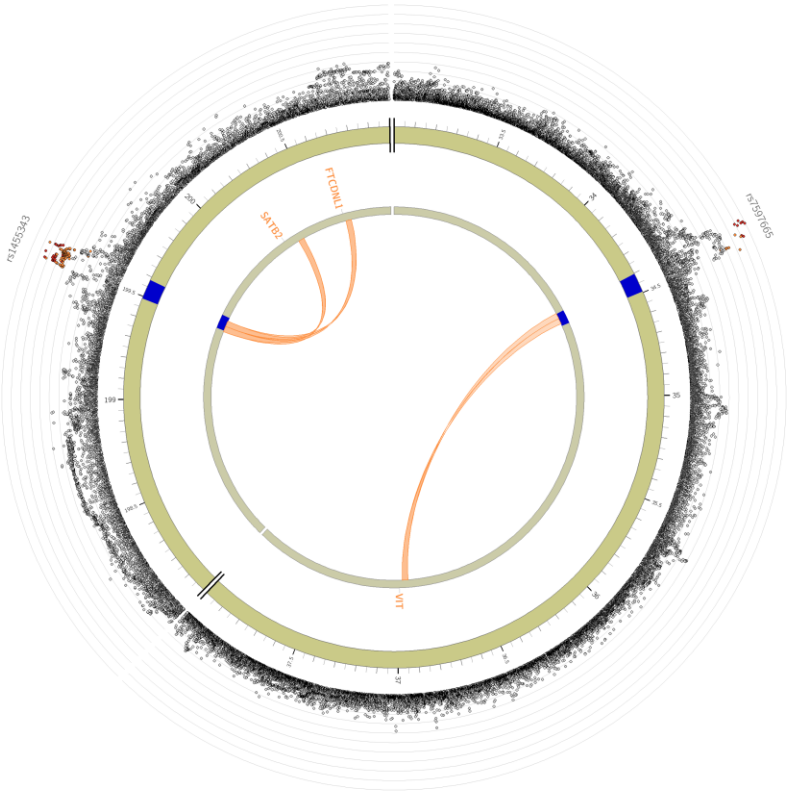


Figure S5c. Circos plot for email contact chromosome 3

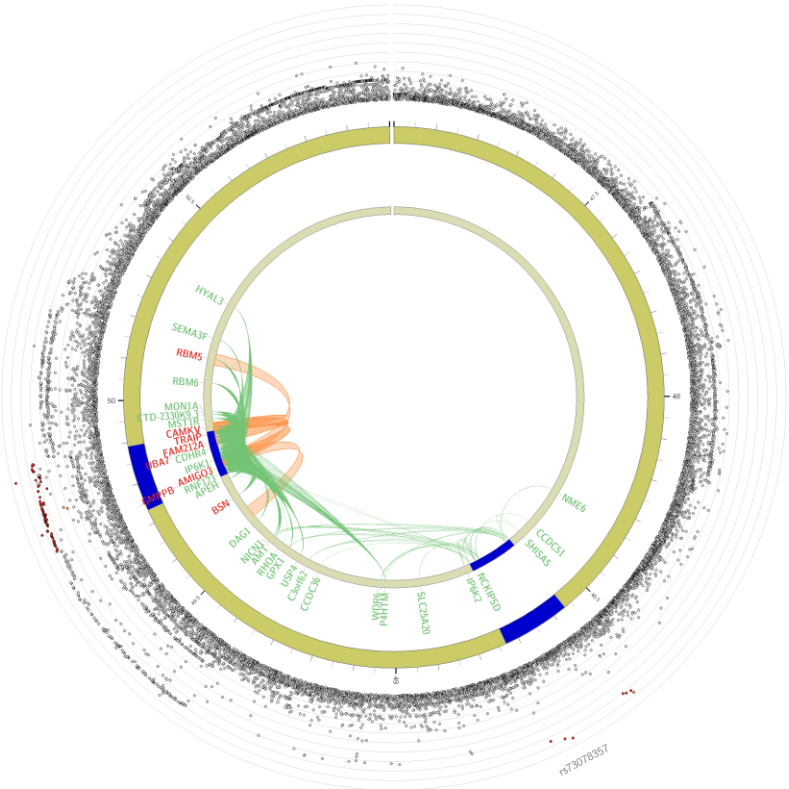


Figure S5d. Circos plot for email contact chromosome 5

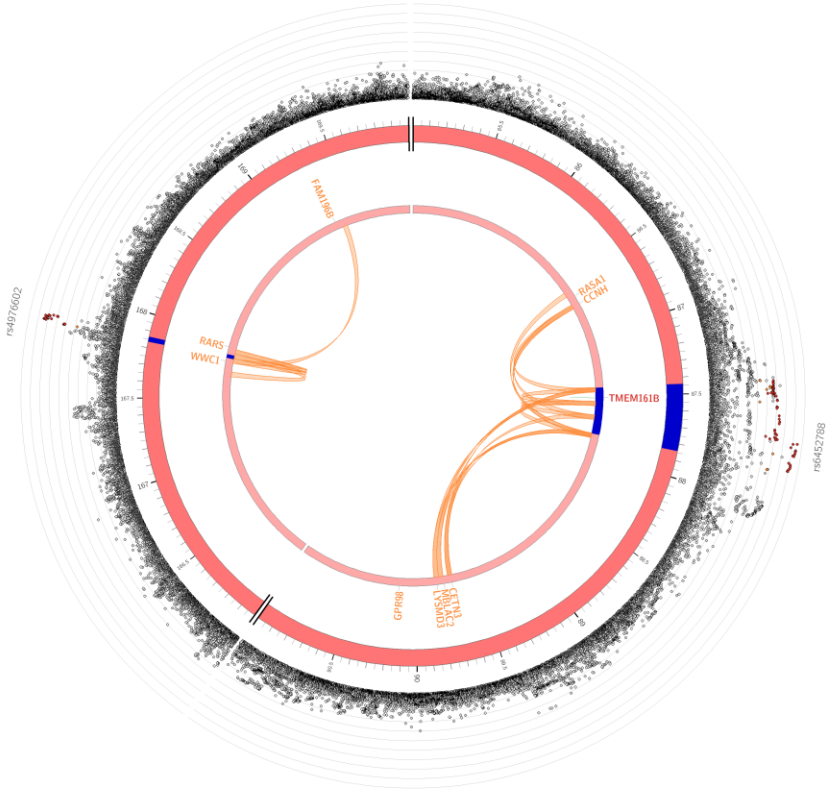


Figure S5e. Circos plot for email contact chromosome 6

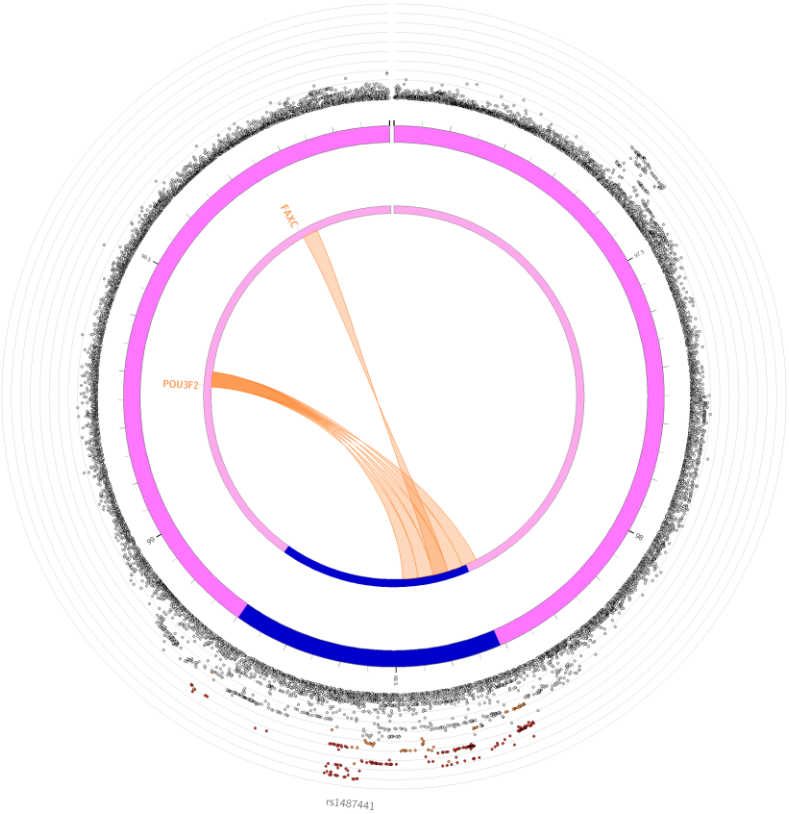


Figure S5f. Circos plot for email contact chromosome 18

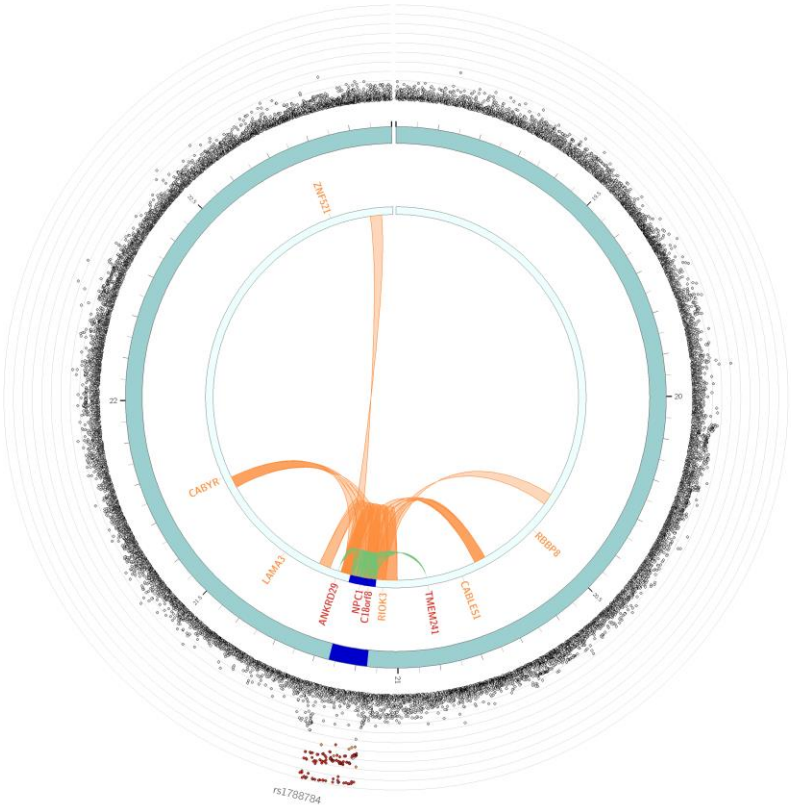


Figure S6a. Circos plot for MHQ data chromosome 1

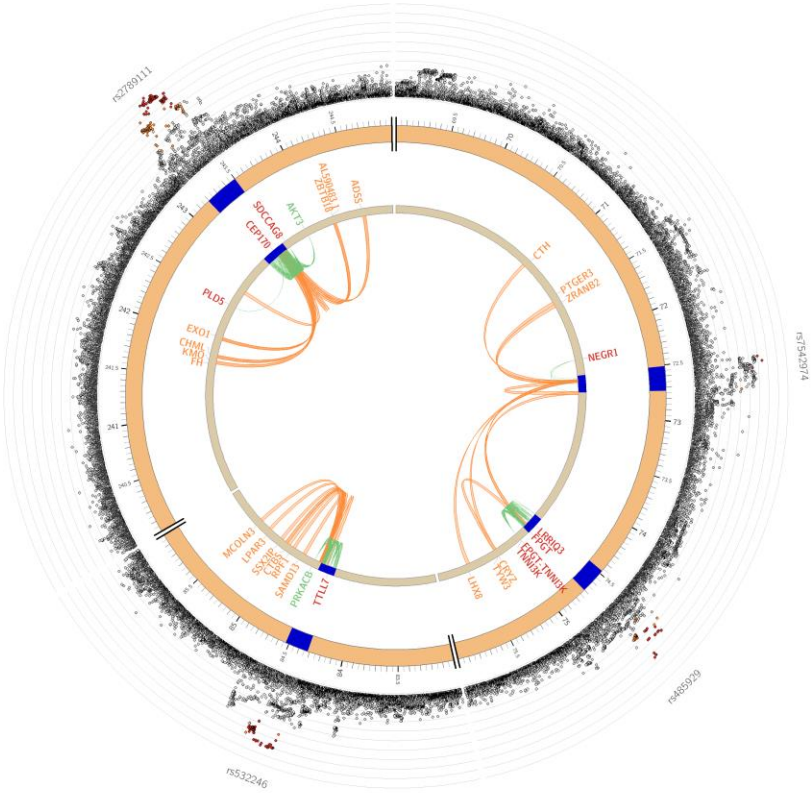


Figure S6b. Circos plot for MHQ data chromosome 2

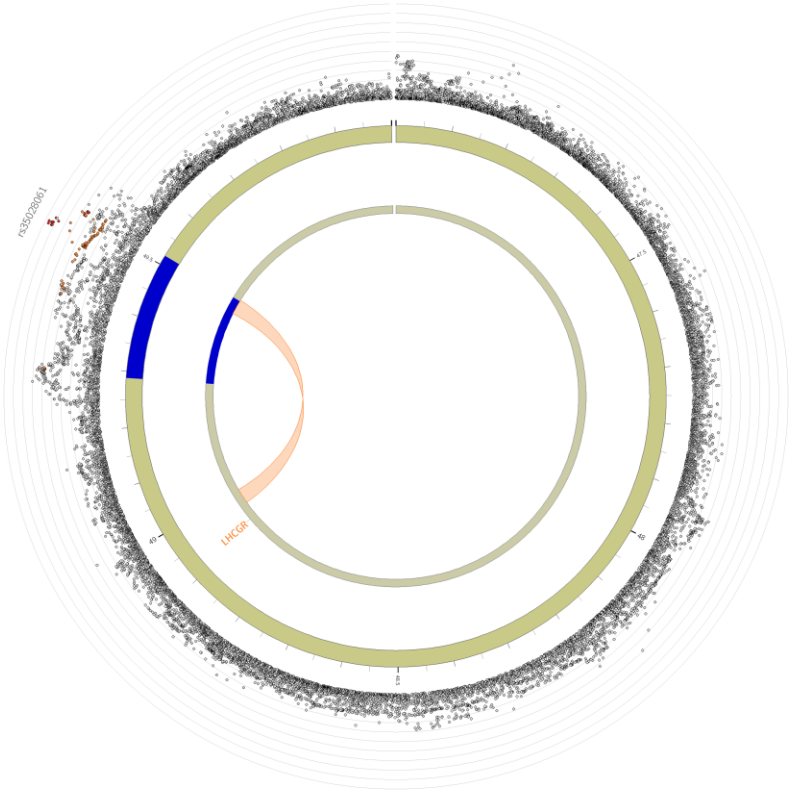


Figure S6c. Circos plot for MHQ data chromosome 3

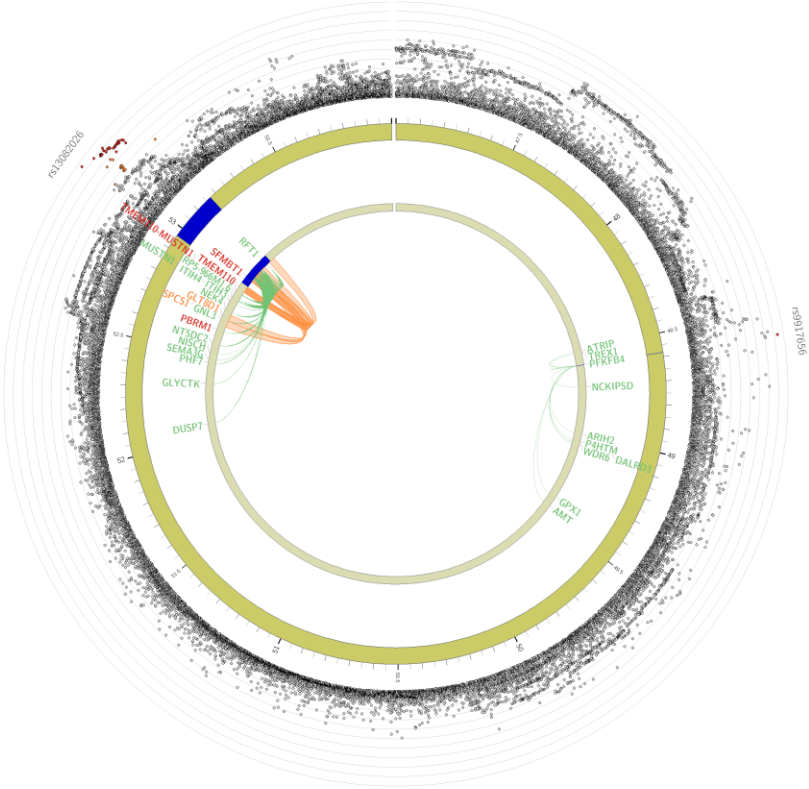


Figure S6d. Circos plot for MHQ data chromosome 4

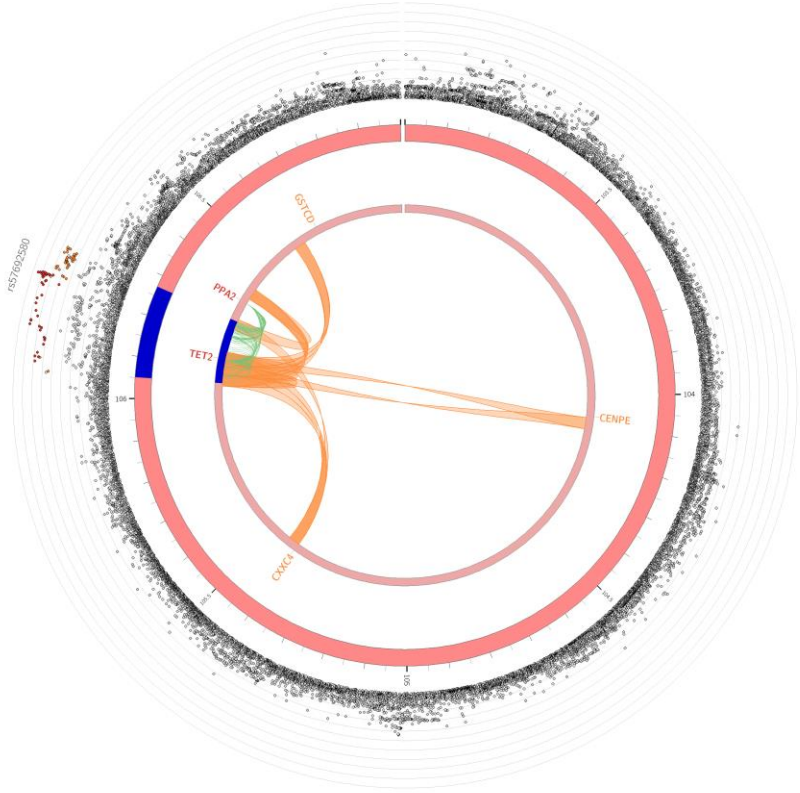


Figure S6e. Circos plot for MHQ data chromosome 5

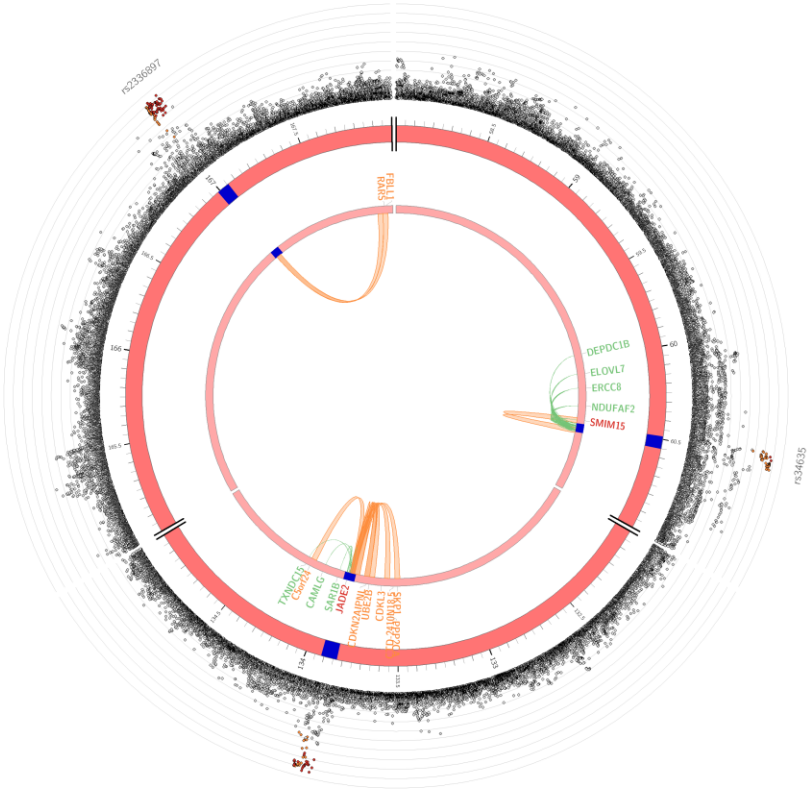


Figure S6f. Circos plot for MHQ data chromosome 6

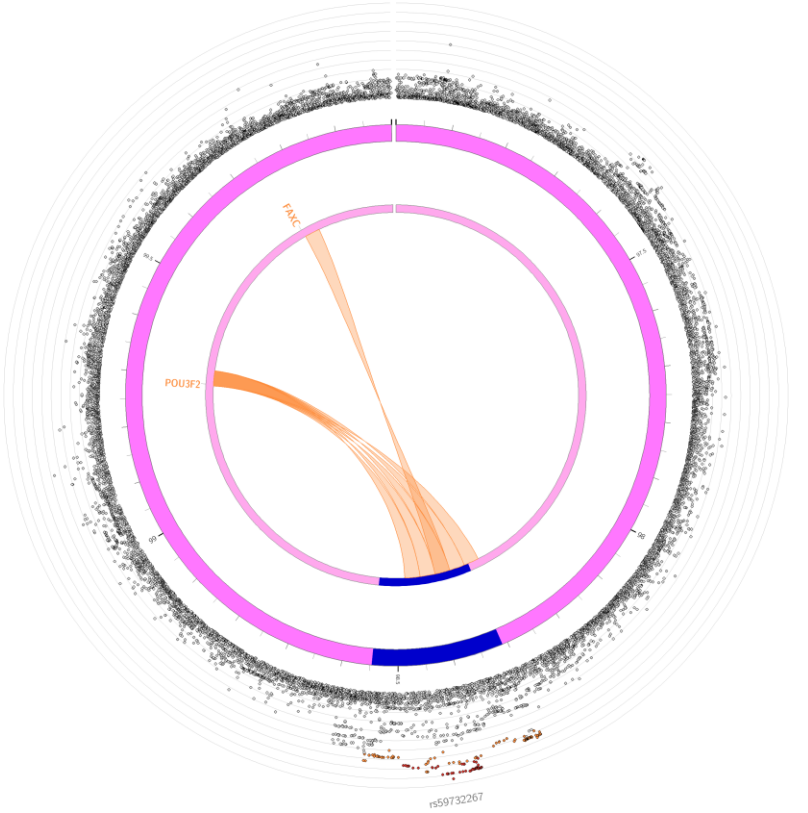


Figure S6g. Circos plot for MHQ data chromosome 8

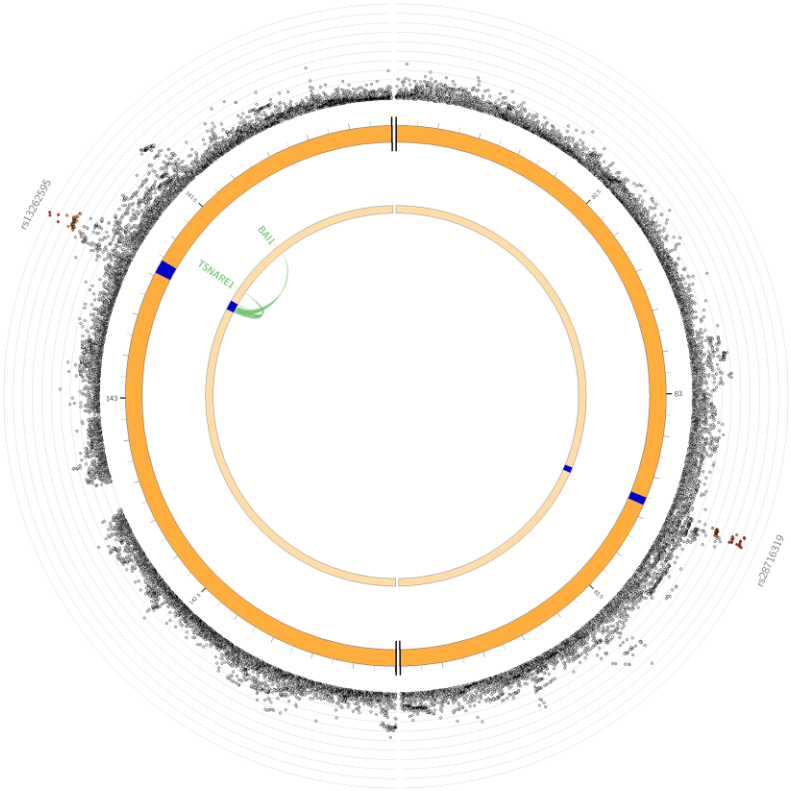


Figure S6h. Circos plot for MHQ data chromosome 9

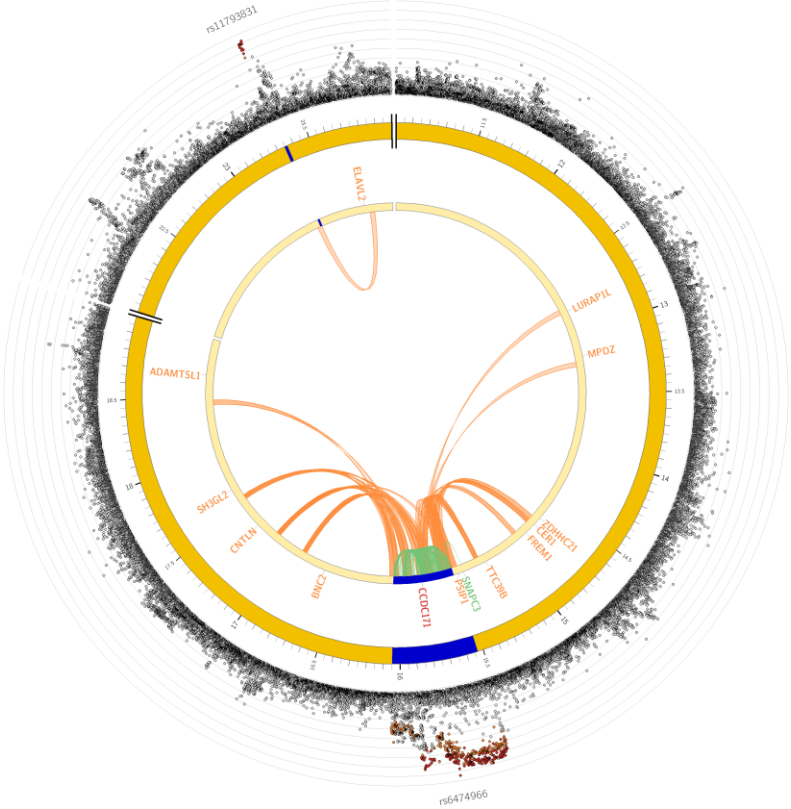


Figure S6i. Circos plot for MHQ data chromosome 11

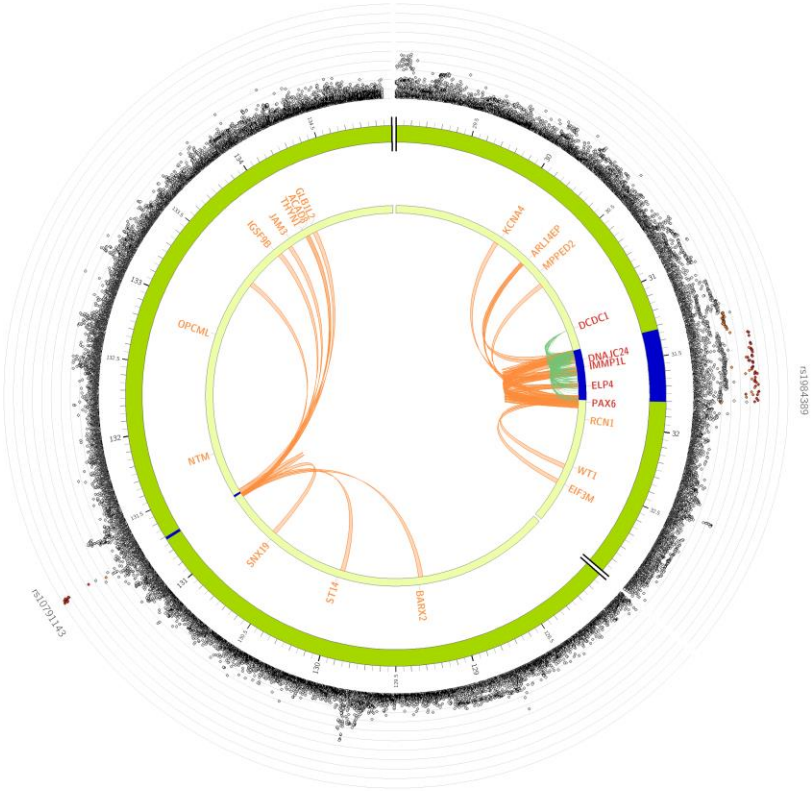


Figure S6j. Circos plot for MHQ data chromosome 16

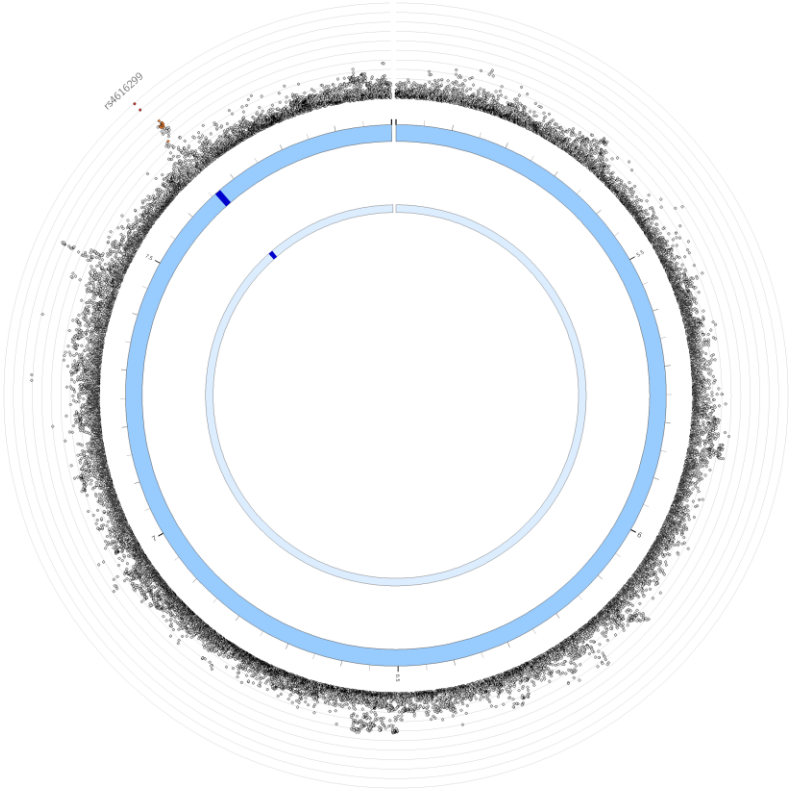


Figure S6k. Circos plot for MHQ data chromosome 17

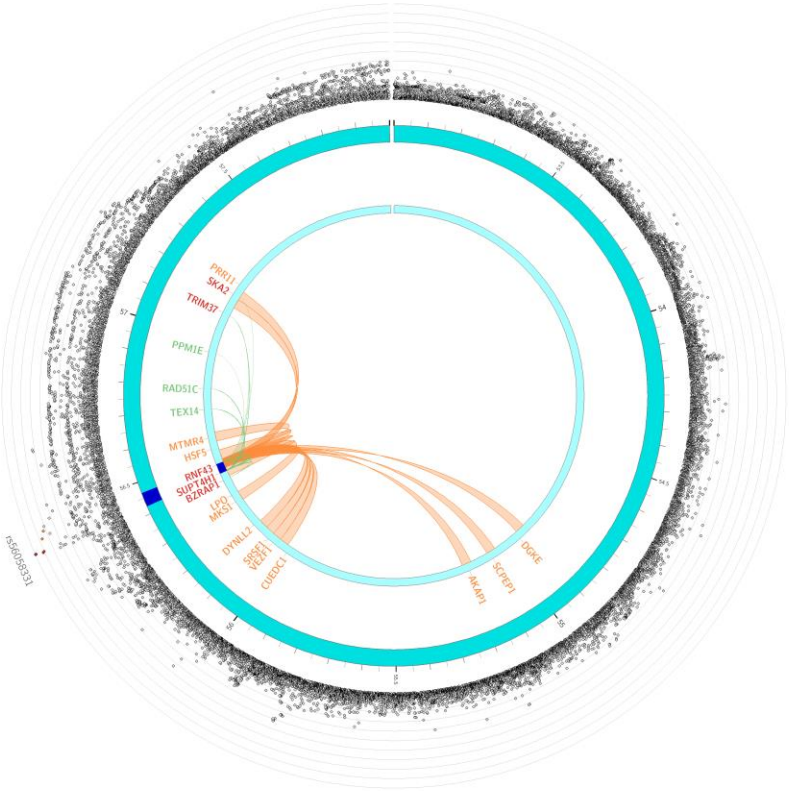


Figure S6l. Circos plot for MHQ data chromosome 18

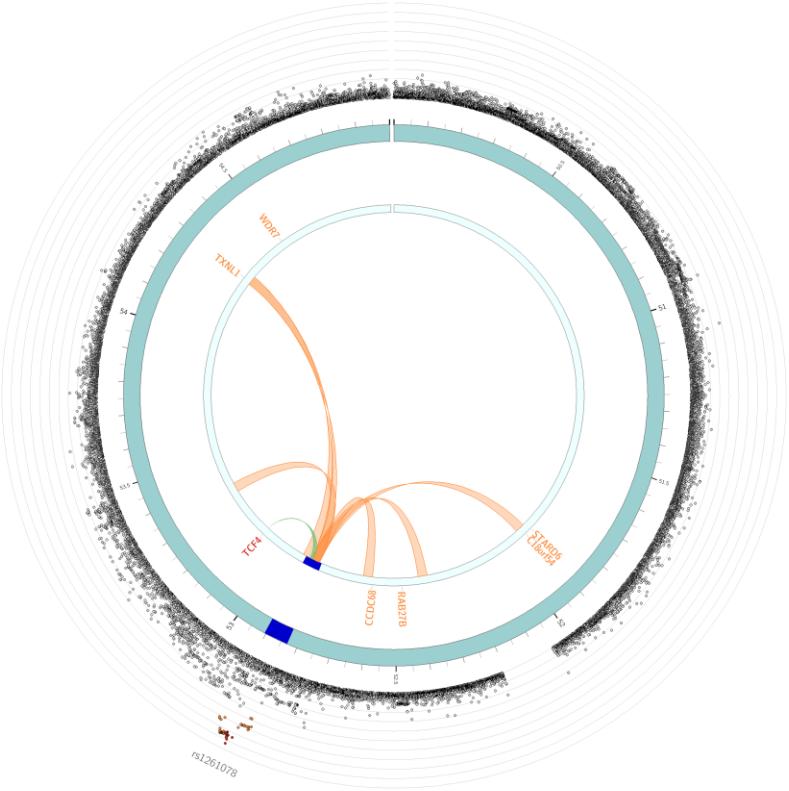


Figure S6m. Circos plot for MHQ data chromosome 19

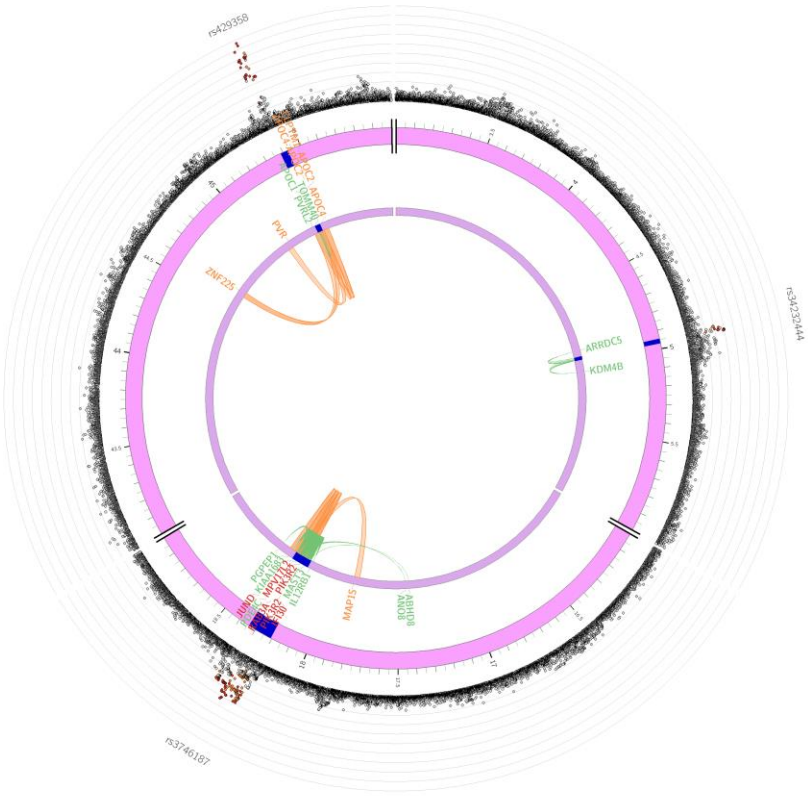


Figure S7. Comparison of effect sizes (as odds ratios) from top independent SNPs in the MHQ GWAS (x axis) compared to the MHQ GWAS whose deaths were reported before the recontact assessment period (y axis). Each SNP is plotted as overlaid with two sets of confidence intervals bars: 95% confidence interval (green) for assessing whether the effect size differs between the two GWAS; 99.999995% confidence interval (orange) for assessing whether the effect size differs from 1.0.

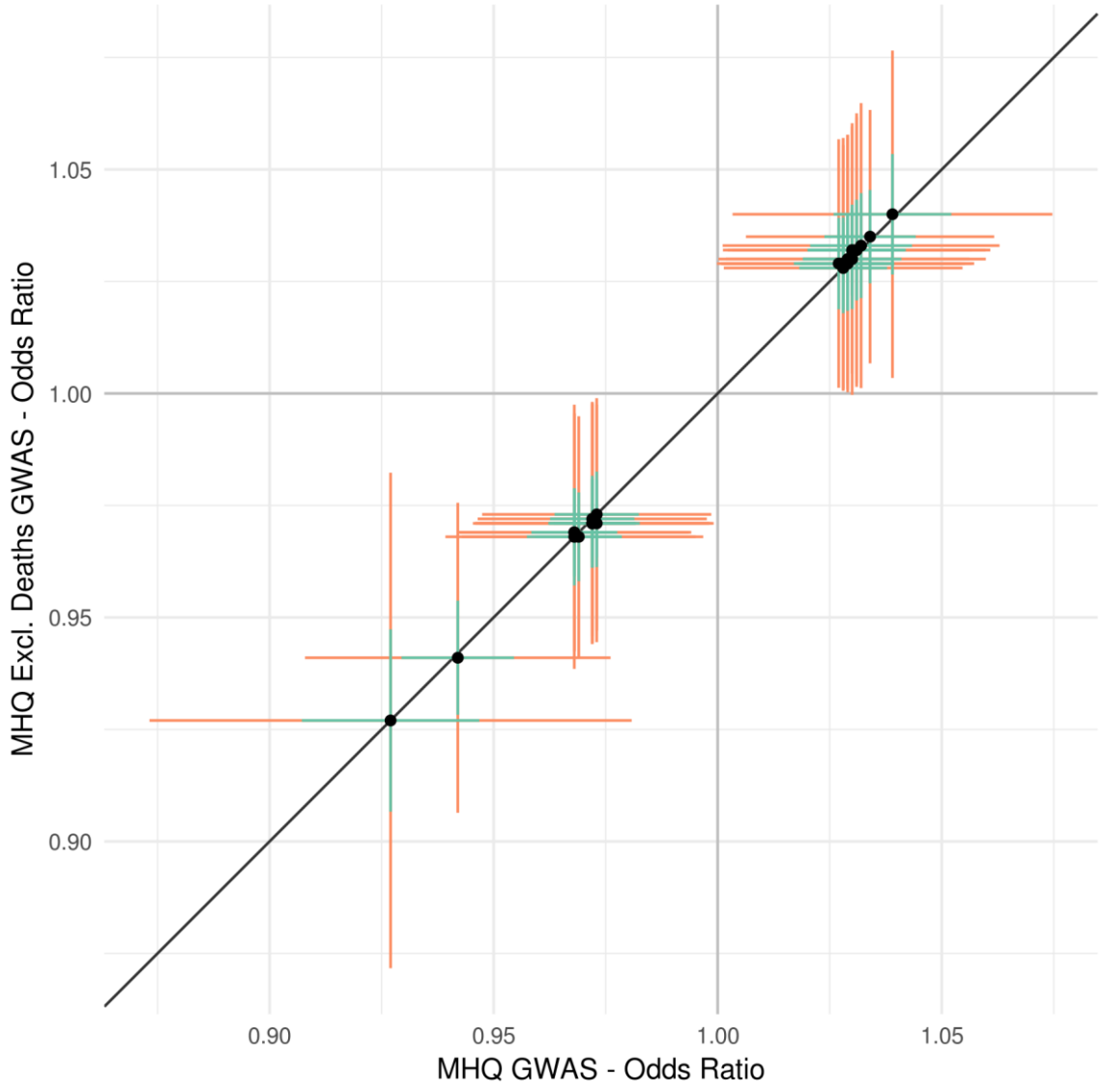


Figure S8. Filtering of the UK Biobank sample for genetic analysis. White British ancestry was determined by four-mean clustering of genetic principal components. Study overlap used genotype checksums to check for overlap with Psychiatric Genomics Consortium Major Depressive Disorder and Generation Scotland cohorts.